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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,342	09/21/2005	Dean Y Li	UUTH-P01-010	2504

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	PAPER NUMBER
1647	

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12/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,342	LI ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9 and 19-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0909*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 09/24/2009 has been entered. Claims 7–9 and 19–21 are pending and being examined.

Interview Summary

In a telephone interview on 12/04/2009 with Attorney Samuel Webb the examiner proposed the following claim amendments.

> 1-6. (Canceled)
>
> 7. A method of inhibiting migration of human microvascular endothelial cells (HMVECs) expressing a native Robo-4 receptor, the method comprising exposing said HMVECs to a ~~Slit-~~ Slit2 ligand or a HMVEC migration inhibiting fragment thereof, wherein exposing said HMVECs to said Slit ligand inhibits migration of said HMVECs.
>
> 8. (Canceled)
>
> 9. The method of claim[[8]] 7, wherein exposing said HMVECs to a Slit2 ligand comprises exposing said HMVECs to a human Slit2 ligand or a HMVEC migration inhibiting fragment thereof.
>
> 10-22. (Canceled).

Although the examiner and Mr. Webb agreed to the proposed changes, the examiner is withdrawing the indicated allowability of the proposed claims in view of the newly discovered reference(s) to Geng (U. S. Publication No. 20030236210). Rejections based on the newly cited reference(s) follow.

Maintained formal matters, objections, and/or rejections:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7–9 and 19–21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the migration of HMVECs in vitro using Slit2 ligand, does not reasonably provide enablement for a method of inhibiting the migration of HMVECs without regard to the system in which the Slit ligand is employed or for a method of preventing angiogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Response to Arguments

Applicant argues that:

> At the time of filing, upon review of the teachings and guidance provided by the as-filed specification, one of ordinary skill in the art would have all the information needed to practice the claimed invention without undue experimentation. ... When the experimental results detailed in the specification are combined with the specific teachings provided by the specification, ...one of ordinary skill in the art would be equipped with information sufficient to practice the full scope of the methods recited in the pending claims.
>
> ...the enablement requirement does not dictate that the specification provide working examples describing every embodiment of a claimed invention, only that the specification as a whole allow one of ordinary skill to practice the invention without undue experimentation. (See, M.P.E.P. § 2164.02). Again, Applicants respectfully submit that the teachings of the specification, particularly in light of the experimental evidence provided therein, specifically enable the subject matter recited in the pending claims. Moreover, the evidence used to support the assertion that the art

> pertaining to the claimed subject matter is particularly unpredictable is either not applicable and not relevant.

Applicants' arguments have been fully considered but they are not persuasive. The examiner did not make a requirement that the specification provide working examples of every embodiment of the claimed invention. However, the examiner did indicate that the claims encompass *in vitro* and *in vivo* methods of inhibiting the migration of HMVECs and/or preventing angiogenesis whenever and wherever angiogenesis is occurring by activating a Robo4 receptor with any Slit or with Slit2. The full scope of a claim must be enabled. The one working example in the specification is limited to disclosing that Slit2 inhibits the migration of HMVECs expressing Robo4 (paragraph [0045]) in an in vitro cell migration assay (Figure 7). There are no working examples wherein angiogenesis is prevented. The examiner did find that Applicants' enablement of one mode of practicing the invention (an *in vitro* method of inhibiting the migration of HMVECs expressing a native Robo4 receptor with slit2) was not sufficient to enable the full scope of the claimed invention because the rejection of record cited references that found results counter those disclosed and claimed in the present application, and held that there is a lack of predictability in the art, angiogenesis and vascular guidance are complex, and the working examples and guidance in the specification are limited.

Applicants argue that:

> Enablement must be assessed as of the time of filing. ...[E]xaminers, as a general rule, should not use post-filing date references to demonstrate an application is not enabling. ...Such references are simply not applicable to an assessment of enablement as of the time of filing... .

> ...there is a limited exception that allows for consideration of post-filing date references in an analysis under 35 U.S.C. § 112, First Paragraph, ... Specifically, a post-filing date reference may be used to assess enablement where that reference establishes that, after the filing date, it was not possible to carry out the claimed invention. ...However, that is simply not the case for the subject matter recited in pending claims 7 through 9 and 19 through 21. The Office Action cites two post-filing date references in support of the enablement rejection. However, neither of these references is relevant to the subject matter recited in the pending claims, and they certainly do not establish that it is not possible to carry out the claimed subject matter.
>
> ...the teachings of Wang are directed to Robo1 receptors, not Robo4 or how the Robo4 receptor interacts with Slit peptides. Nothing in Wang establishes that it is not possible to carry out the subject matter recited in the pending claims. Moreover, the teachings in Wang run contrary to accepted literature regarding the function of Robo1 in non-neural cells. (See, The neuronal repellant Silt inhibits leukocyte chemotaxis induced by chemotactic factors, Wu JY, Feng L, Park HT, Havlioglu N, Wen L, Tang H, Bacon KB, Jiang Zh, Zhang Xc, Rao Y. Nature. 2001 410(6831):948-52)). The teachings of Wang, consequently, are not relevant to systems requiring the presence of Robo4, they are at odds with long-accepted teachings in the art, and they do not establish that it is not possible to carry out the claimed subject matter.
>
> ...Okada also lacks guidance or results regarding the interactions of Robo4 with Slit ligands. The self-expressed goal of the work reported in Okada was to dissect the mechanism of cell-type specific expression of the Robo4 promoter. The work described in Okada was not concerned with the interaction of Slit ligands with Robo4, and nothing in Okada establishes that it is not possible to carry out the subject matter recited in the pending claims. Therefore, the teachings of Wang and Okada, whether considered alone or in combination, are not relevant to an enablement analysis for the subject matter recited in pending claims 7 through 9 and 19 through 21. These references were not only published well after the filing date of the present application, but the teachings they provide are not relevant to the subject matter recited in the rejected claims. Again, Applicants respectfully request that the rejection of claims 7 through 9 and 19 through 21 under 35 U.S.C. § 112, First Paragraph, be withdrawn.

Applicants' arguments have been fully considered but they are not persuasive.

The examiner uses Wang (Cancer Cell. 2003 Jul:4(1):19-29) to establish that, after the

filing date, it was not possible to carry out the full scope of the claimed invention because Wang's results indicate that Slit2 can promote angiogenesis and microvessel migration *in vivo*. Although Wang is concerned with Robo1 signaling, the results of Okada (Circ Res. 2007 Jun 22;100(12):1712-22) indicate that microvascular endothelial cells express a native Robo-4 receptor, and that Wang's results, that are opposite to those claimed, are not due to a lack of Robo-4 expression in Wang's experimental system. The examiner believes Okada is relevant in this regard.

The examiner is unaware of any requirement that Wang's results must be in agreement with, or analogous to, results regarding the function of Robo1 in non-neural cells, specifically leukocytes.

Applicants argue that:

> To the extent, the Examiner seeks to continue utilizing post-filing date references as support for rejections of the claims pending in this application, Applicants would like to draw the Examiner's attention to three articles that have been published or, in the case of the third article, are ready for print: 1) Robo4 is a vascular-specific receptor that inhibits endothelial migration, Park, KY, Morrison, CM, Sorenson, LK, Chien, CB, Wu JY, Li DY (2003); Dev Bio 261:251-26; 2) Robo4 stabilizes the vasculature by inhibiting angiogenesis and endothelial hyperpermeability, Jones C, London N, Park K, Chen H, Stockton R, Nishiya N Ginsberg M, Zhang K, and Li DY (2008); Nature Medicine 14(4):448-53; and 3) Slit2-Robo4 signaling promotes vascular stability by blocking Arf6 activity, Jones CA, Nishiya N, London NR, Zhu W, Sorensen LK, Chan A, Lim C J, Chen H, Zhang Q, Schultz PG, Hayallah AM, Thomas KR, Famulok M, Zhang K, Ginsberg MH, Li DY (2009, in press); Nature Cell Biology. Full copies of these articles are provided with an IDS filed simultaneously herewith. These articles illustrate that the teachings of the present application enable the subject matter recited in the pending claims, and the combined teachings provided by these three documents highlight that, it is, in fact, possible to carry out the subject matter recited in the pending claims in accordance with the teachings found in the present application.

Applicants' arguments have been fully considered but they are not persuasive. Applicants' do not specifically point to any specific teachings in these references. However, the references have been considered. ,

Park (Dev Biol. 2003 Sep 1;261(1):251-67) does not provide any *in vivo* results.

Jones (Nat Med. 2008 Apr;14(4):448-53) and Jones (2009) are post-filing date references disclosing a later existing state of the art which did not exist on the filing date of the present application. Specifically, Jones (2008) demonstrates that Robo4 mediates Slit2-dependent inhibition of VEGF-165–induced retinal endothelial cell hyperpermeability in vitro and in vivo (paragraph bridging pages 449-450) and that Robo4 signaling inhibits VEGF-165–dependent endothelial migration, tube formation and permeability (page 451, paragraph bridging left and right columns). Jones (2009) demonstrates that inhibition of Arf6 activity in vivo phenocopies Robo4 activation by reducing pathologic angiogenesis in choroidal and retinal vascular disease and VEGF-165 (vascular endothelial growth factor-165)-induced retinal hyperpermeability (Abstract).

As indicated previously, the claims encompass *in vitro* and *in vivo* methods of inhibiting the migration of HMVECs and/or preventing angiogenesis whenever and wherever angiogenesis is occurring by activating a Robo4 receptor with any Slit or with Slit2. The results of Wang (Cancer Cell. 2003 Jul:4(1):19-29) indicate that Slit2 can promote angiogenesis and microvessel migration *in vivo*. Therefore, the correlation between the disclosed in vitro effects in the present application, the full scope of the

claimed invention and those results seen in in vivo is insufficient to enable the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19–21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite because it lacks a process step which clearly relates back to the claim preamble and it is unclear whether preventing angiogenesis is achieved; an intended use is not the same as achieving a result; it is unclear what result of the process can be inferred. Claims 20 and 21 depend from claim 19, and thus share this defect with claim 19. The metes and bounds are not clearly set forth.

Applicants argue that:

> ...Applicants have amended claim 19 ...such that the claim refers to a method of preventing angiogenesis requiring the migration of HMVECs, with a process step included in the method that requires inhibiting migration of HMVECs expressing a native Robo-4 receptor. Applicants respectfully submit that claim 19 and claims 20 and 21, which depend therefrom, now more clearly express a method comprising a process step relating back to the relevant preamble.

Applicants' arguments have been fully considered but they are not persuasive. It is unclear if angiogenesis is prevented and HMVEC migration is inhibited, or if only HMVEC migration is inhibited. The metes and bounds are not clearly set forth.

New Formal Matters, Objections and/or Rejections

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7–9 and 19–21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geng (U. S. Publication No. 20030236210) in view of Goldberg (U. S. Patent No. 5,480,975).

Geng discloses a method for treating a disease or disorder associated with Slit2 mediated angiogenesis in a subject, which method comprises enhancing Slit2-Slit2 receptor interaction in a subject to a level sufficient to prevent or treat a disease or disorder associated with Slit2 mediated angiogenesis in said subject [0008] with a composition comprising a substance that enhances Slit2-Slit2 receptor interaction [0009], wherein the disease is hypoxia ([0063]; claim 15).

Geng claims priority to U.S. Provisional application No. 60362485. In U.S. Provisional application No. 60362485 Geng teaches a method of stimulating angiogenesis with a Slit protein for the treatment of ischemia and hypoxia, leukocyte trafficking and recruitment, hemostasis, wound healing and vascular leaky syndrome (U.S. Provisional application No. 60362485, claim 4). Geng shows that human slit2

induces the migration and tube formation of HUVECs (U.S. Provisional application No. 60362485, page 3, full paragraphs 1-2). However, Geng does not explicitly teach the administration of slit2 to humans.

The stimulation of angiogenesis in hypoxic areas of human patients is well known in the art. See, for example, Goldberg (U. S. Patent No. 5,480,975), column 2, lines 25-35; column 4, lines 10-30; claim 14). Goldberg does not teach the administration of human slit2.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to stimulate angiogenesis with human Slit2 protein for the treatment of hypoxia, as taught by Geng, and to modify that teaching by treating hypoxic areas of human patients, as taught by Goldberg, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to stimulate angiogenesis in hypoxic areas of human patients.

The claims encompass the administration of slit2 to humans. Inhibiting the migration of HMVECs expressing a native Robo-4 receptor would naturally flow from following the teachings of Geng in view of Goldberg.

The claimed method is obvious because the administration of human slit2 to humans is suggested by Geng in view of Goldberg. Applicants' recognition that slit2 inhibits the migration of HMVECs expressing a native Robo4 receptor does not render nonobvious an otherwise known invention. Granting a patent on the discovery of an unknown but inherent function (here inhibiting the migration of HMVECs expressing a

native Robo4) would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. The fact that applicants have recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. The recitation of an additional advantage associated with doing what the prior art suggests does not lend patentability to an otherwise unpatentable invention. Furthermore, the reason or motivation to modify the reference may often suggest what an inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. While there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention.

For this rejection, claims 19–21 have been construed as only requiring inhibition of the migration of HMVECs.

The invention is prima facie obvious over the prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19–21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support for the limitation "angiogenesis requiring the migration of HMVECs" cannot be found in the disclosure, as originally filed, which raises the issue of new matter.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY NICKOL, CAN BE REACHED AT (571)272-0939.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-0835.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID S ROMEO/
PRIMARY EXAMINER, ART UNIT 1647

DSR
DECEMBER 7, 2009